OREGON DUR BOARD NEWSLETTER®
Commonly Misused Drugs That Are Not Addicted
http://pharmacy.oregonstate.edu/drug-policy/index.cfm

June 2009 Volume 11, Issue2

An Overview of the Safety of Methadone Use and Recommendations for Judicious Use

By Domenica Oberholtzer, PharmD, CGP, OSU College of Pharmacy

Although methadone has had a comparable safety and efficacy profile to morphine for use in chronic non-malignant and cancer pain, its safety is of increasing concern due to its long and variable half-life and associated risk of QT interval prolongation.[1,2,3,4,5,6] This prompted a FDA safety alert in November 2008 resulting in a black box warning highlighting the risk of sudden death and cardiac arrhythmias secondary to QTc prolongation and torsades de pointes. A recent analysis of the Oregon fee-for-service Medicaid methadone use revealed that 10% of the 532 patients who received methadone from 12/1/07 – 11/30/08 were receiving a dose associated with a higher risk of QTc prolongation (Table 1). Given this situation, methadone should not be considered a first line agent and clinicians prescribing methadone should be knowledgeable about its unique pharmacokinetic properties, drug-drug interactions and toxicities.[7,8,9,10,11] Patients must be carefully selected and the drug carefully prescribed and monitored.

Table 1. – Oregon FFS Methadone Use Summary per Patient*

n = 532		Range
Mean Claim Count per Patient	9	(1-38)
Mean Total Days Supply per Patient	226	(1-780)
Mean Daily Dose per patient	62	(2.5-719)
Unique patients with mean dose >120mg/day	55	10%

*http://pharmacy.oregonstate.edu/drug_policy/pages/dur_board/evaluations/articles/Methadone_DUE.pdf

A Summary of Dosing and Safety Considerations[7]

- Elimination half-life is highly variable (3-128 hours) and does not reflect the duration of analgesia. At the mean half-life of approximately 60 hours it would take 12 days to reach steady state. Thus plasma levels accumulate and adverse effects are delayed 1-2 weeks from initiation.
- Morphine Equivalent (ME) conversion ratios vary by ME dose (< or > 200mg), patient genetics, route, acute vs. chronic dosing and are not bi-directional. When moving from methadone to morphine it is important to allow 28 days for methadone to clear.
- Methadone is predominantly metabolized by CYP C3A4 but also by CYP 2B6 and is heavily protein bound; therefore there are many potential drug interactions.
- Methadone prolongs the QTc interval through its effects on cardiac repolarization. It is also a negative inotrope. Both effects contribute to sudden cardiac death events even in the absence of structural cardiac defects.

Prescribing Recommendations

- Opioid naïve or patients receiving codeine preparations: start at low dose and increase slowly[7]
  - 2.5 mg BID-TID; upward titration by 2.5 mg q8h no sooner than weekly
- Conversion from other opioids
  - Starting dose not to exceed 40 mg/day; upward titration no sooner than weekly.[8]
  - Use short-acting opioid for breakthrough pain until optimum dose reached[8]
- QTc Evaluation for at risk patients[9,10]
  - High doses such as above 60 mg/day.
  - Females (longer QTc interval)
  - Family history of "long QTc syndrome"; syncope/sudden death
  - Electrolyte depletion (especially potassium)
  - Concomitant use of CYP 3A4 inhibitors or QTc prolonging drugs (Table 2)
  - Structural heart disease, arrhythmias, syncope
  - ECG screening and discontinuation of methadone recommended with QTc intervals near 400-500 ms.

Table 2. Possible methadone drug interactions causing QTc prolongation or cardiac arrhythmias

Type	Drug or Drug Class	Drug Interaction Classification
CYP 3A4 Inhibitors	Phenothiazines (promethazine, prochlorperazine, chlorpromazine)	Contraindicated
	Ziprasidone	Contraindicated
	Amiodarone	Avoid Use/Use Alternative
	Macrolides (azithromycin, clarithromycin, erythromycin)	Avoid Use/Use Alternative
	Quinolones (ciprofloxacin)	Avoid Use/Use Alternative
	Tricyclic antidepressants	Avoid Use/Use Alternative
QTc Pro-longing Drugs	Phenothiazines (promethazine, prochlorperazine, chlorpromazine)	Contraindicated

Source: Epocrates online database. https://online.epocrates.com. This is not a comprehensive list of possible drug-drug interactions. Additional drug-drug interactions may be viewed at Epocrates online database. https://online.epocrates.com.

ECG monitoring

- It has been recommended that an ECG be done at baseline and after a recent dosage increase, in the presence of liver dysfunction, and as otherwise clinically indicated.[9,10,11,12,13,14,15]
- There is much debate on how this can be accomplished in different settings (i.e heroin treatment clinics). Recently a Guideline for QTc Interval Screening in Methadone Treatment was published in the Annals of Internal medicine. It was suggested that ECG should be done prior to initiation of methadone, within 30 days of starting treatment then annually thereafter. In addition, ECG was recommended with doses exceeding 100 mg/d or in the case of unexplained syncope or seizures while receiving treatment.[9]

Converting to an Alternative Opioid

Patients may benefit from an alternative medication to methadone when risk factors and/or drug-drug interactions outweigh the risks over the benefits in pain management. Also, it is important to be aware that not all pain is responsive to opioids and be prepared with alternative therapies to prevent continued use or escalating doses to potentially harmful levels. When performing the conversion it is imperative to keep in mind that one is calculating the total daily dose and this must be adjusted to accommodate for dosing intervals, tablet strengths, and clinical setting. Also, it is important to recognize that conversion ratios are inexact, and dose adjustments for incomplete cross tolerance must be accounted for. Table 3 lists other important factors to consider and Table 4 provides some additional resources.

Table 3. Points to consider about equianalgesic conversion ratios[7]

A number of equianalgesic dosing tables underestimate the potency of methadone[8]
Conversion ratios in many equianalgesic dosing tables do not apply to repeated doses of opioids
The morphine-to-hydromorphone-to-methadone conversion ratio increases (i.e., the potency of methadone increases) as the previous dose of morphine or hydromorphone increases[9]
Conversion ratios may not be bi-directional (i.e., the morphine-to-methadone conversion ratio may not be the same as the methadone-to-morphine ratio)[10]
There may be large interpatient variability in the equianalgesic conversion ratio; a single ratio may not be applicable to all patients[11]
The use of high but ineffective doses of previous opioid may result in overestimation of the equivalent dose of methadone
The relative analgesic potency ratio of oral to parenteral methadone is 2:1[12] however, confidence intervals are wide

Management of Cancer Pain, Clinical Practice Guidelines, AHCPR, 1994[13]; Cancer pain: a monograph on the management of cancer pain, Health & Welfare Canada, 1984[14]; Twycross, 1988[15]; Levy, 1996[16]

- The oral morphine to oral methadone conversion ratio may be unexpectedly much higher in patients who previously received very high doses of morphine.[17,18]

Bruera, 1996[19]

- Estimated ratio based on single-dose, double-blind, double-dummy, cross-over studies in patients with moderate to severe cancer pain.[20]

Table 4. Resources on Converting between Opioids

Suggestions for Converting among Opioids:
http://pharmacy.oregonstate.edu/drug_policy/prescriber_tools/Opioid_Conversion_Suggestions.pdf

Equianalgesic dose calculators:
http://www.globalrph.com/narcoticonv.htm
(prescriber must fill in box with % dose reduction to adjust for incomplete cross tolerance)
http://www.hopweb.org
(site states that dose calculated by formula must be decreased by about 30% to adjust for incomplete cross tolerance.)

Additional information on opioid conversions:
http://www.cancer.gov/cancertopics/pdq/supportivecare/pain/HealthProfessional/121.cdr#Section_121.

Educating the Patient

A well-informed patient is better able to communicate with his or her prescriber about possible adverse effects that may be occurring. Consider the following key pieces of knowledge to share with your patients:

- The initial dose may not provide immediate pain relief and a breakthrough pain medication may need to be utilized. To aid in dose titration, have the patient keep a pain diary with a record of all doses of breakthrough pain medication used.
- Provide reassurance that the optimal dose will be pursued via titration, but set realistic expectations since average pain relief is about 30%.[15,16]
- Advise that methadone's analgesia will increase over time, about 1 week after initiation or after a change in dose. In other words, pain relief during the last few days of that week will be greater than at the first few days of the week.
- Emphasize the need for monitoring and communication during titration and maintenance periods and instruct patients on what steps to take if increasing or intolerable side effects occur. Patient education materials on use of methadone and recognition of side effects are readily available from Substance Abuse and Mental Health Administration's (SAMHSA) and the FDA at:
  http://www.dpt.samhsa.gov/methadonesafety/print_materials.aspx.
- An opioid risk tool is available for prescribers which can aid in facilitating discussion of issues related to use and mis-use of opioids. This may be helpful for opioid naïve patients.
  Dr. Lynn Webster, Lifesource Foundation, Salt Lake City, Utah:
  http://health.utah.gov/prescription/pdf/guidelines/ORTwithout_scoring.pdf

Conclusion

While many alternative opioids exist in the management of pain, there are limited options for patients receiving treatment for opioid dependency. Given the potential issues with methadone, its long and variable half-life, time to analgesia, and potential cardiac issues, prescribers must carefully select and monitor patients who receive treatment from this agent. Not only must the patient's medically history be reviewed for potential cardiac complications prior to initiating treatment, but monitoring for adverse effects must be an ongoing process by both the patient and the prescriber.

Reviewers:
Michele Koder, PharmD, CareOregon Assistant Pharmacy Director; Laura DeSimone MS, RPh., Hospice and Pain Group Pharmacist ,Kaiser Permanente; David Labby, MD, PhD., CareOregon Medical Director; Roger Chou, MD, OHSU Associate Professor of Medicine, Division of General Internal Medicine; Therese Hutchinson, Policy & Program Development Specialist,Addictions and Mental Health Division (AMH).

References:

1. Bernstein M. Prescription drugs top Oregon overdose stats. The Oregonian March 31, 2009. Accessed May 2009. http://www.oregonlive.com/news/index.ssf/2009/03/prescription_drugs_top_oregon.html.
2. FDA Public Health Advisory: Methadone Use for Pain Control May Result in Death and Life-Threatening Changes in Breathing and Heart Beat. http://www.fda.gov/cder/drug/advisory/methadone.htm. Accessed May 2009.
3. Chugh SS, Socoteanu C, Reinier K, Waltz J, Jui J, Gunson K. A community-based evaluation of sudden death associated with therapeutic levels of methadone. Am J Med 121:66-71, 2008.
4. Oregon Department of Human Service: Methadone deaths (and distribution) on the rise. CD Summary 52, 2003. http://www.oregon.gov/DHS/ph/pdo/cdsummary/2003/cbd5214.pdf Accessed May 2009.
5. Roger Chou R, Carson S. Drug class review on long-acting opioid analgesics. 2008. http://www.ohsu.edu/drugeffectivenessreports/final.cfm. Accessed June 2009.
6. Nicholson AB. Methadone for cancer pain. Cochrane Database of Systematic Reviews 2007, Issue 4.Art. No.: CD003971. DOI: 10.1002/14651858.CD003971.pub3.
7. Goodman F, Jones WN, Glassman P. Methadone Dosing Recommendations for Treatment of Chronic Pain. United States Department of Veteran Affairs Pharmacy Benefits Management Service, Clinical Guidance / Clinical Recommendations. http://www.pbm.va.gov/clinicalguidance/methadonedosing.aspx. Accessed May 2009.
8. Chou R, et al. Clinical Guidelines for the Use of Chronic Opioid Therapy in Chronic Noncancer Pain. J Pain 2009: 113-130.
9. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MCP. QTc Interval Screening in Methadone Treatment. Ann Intern Med. 2009;150:387-395.
10. Stringer J, Welsh C, Tommasello A. Methadone-associated Q-T interval prolongation and torsades de pointes. Am J Health-Syst Pharm. 2009; 66:825-33.
11. Methadone can cause torsades de pointes. Pharmacits Letter / Prescribers Letter 2002;18(11):181104.
12. White CM, Song JC, Chow MSS. Cardiac arrhythmias. In: Koda-Kimble MA, Young LY, Kradjan WA, et al., eds. Applied Therapeutics: the clinical use of drugs. 8th ed. Philadelphia: Lippincott Williams & Wilkins, 2005.
13. Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. AmJ Cardiol 2005;95:915-8.
14. Ehret GB, Voide C, Gex-Fabry M, et al. Drug-induced long QT syndrome in injection drug users receiving methadone: high frequency in hospitalized patients and risk factors. Arch Intern Med 2006;166:1280-7.
15. Kalso E., Edwards JE, Moore RA, et al. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain 2004;112:372-80.
16. Furaln AD, Sandoval JA, Mailis-Gagnon A, Tunks E. Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects. CMAJ 2006;174(11):1589-94.